Enantioselective Electrophilic Trifluoromethylthiolation of β-Ketoesters: A Case of Reactivity and Selectivity Bias for Organocatalysis

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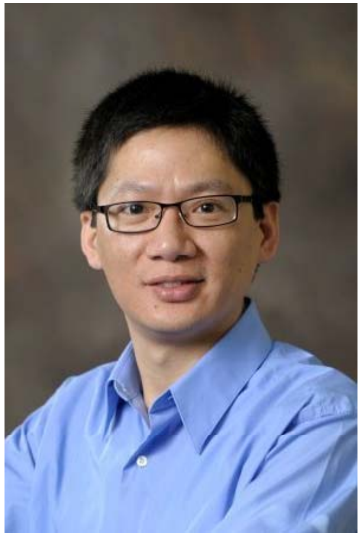
Shen, Q. et al *Angew. Chem. Int. Ed.* **2013**, *52*, 12860

1996年7月 本科毕业于南京大学;
1999年7月 硕士毕业于上海有机化学研究所；
2002年7月 毕业于美国麻省大学Dartmouth分校，获理学硕士学位；
2002年9月至2007年9月 就读于美国耶鲁大学，获哲学博士学位；
2007年10月至2010年3月 于美国伊利诺伊斯大学香槟分校化学系从事博士后研究；
2010年4月至今 中国科学院上海有机化学研究所“中科院百人计划”研究员



沈其龙 研究员
有机氟化学重点实验室(SIOC)

研究领域：
1）过渡金属催化的芳香属卤代物选择性氟代反应方法学研究；
2）含氟氮、膦配体的合成，与过渡金属的配位及其在不对称催化反应中的应用的研究；
3）高选择性的芳香属化合物的碳—氢键活化的方法学研究；
4）具有应用前景的含氟物质及含氟功能材料的合成。

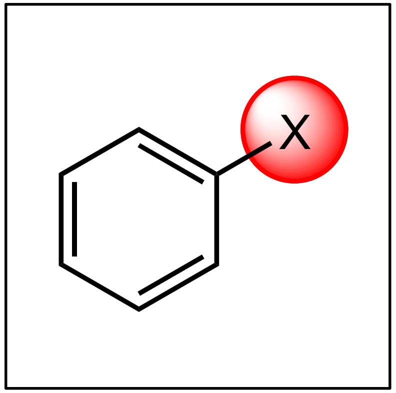
Content

1. Introduction
2. Trifluoromethylthiolation using stable electrophilic trifluoromethylthiolation reagents
3. Asymmetric trifluoromethylthiolation
4. Conclusion

1. Introduction

Table. Lipophilicity Values of some Monosubstituted Benzenes

Substituent (X)	π
H	0.00
F	0.14
CH_3	0.56
Cl	0.71
Br	0.86
CF_3	0.88
OCF_3	1.04
I	1.12
SF_5	1.23
SCF_3	1.44

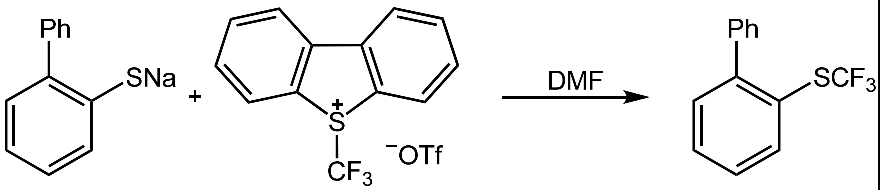


Schlosser, M. et al *Chem. Rev.* **2005**, *105*, 827

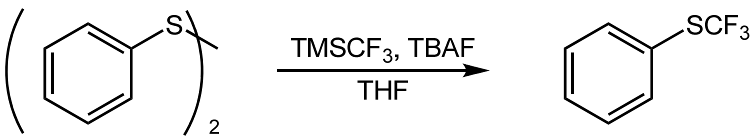
Indirect trifluoromethanesulfanylation	Direct trifluoromethanesulfanylation

Indirect trifluoromethanesulfanylation

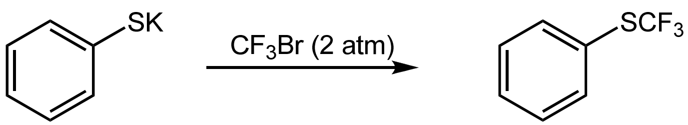
1. electrophilic substitution



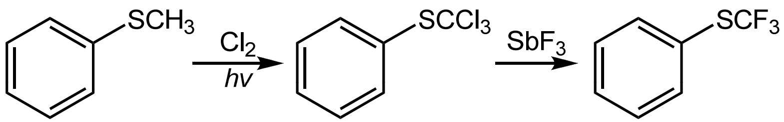
2. nucleophilic substitution



3. radical reaction

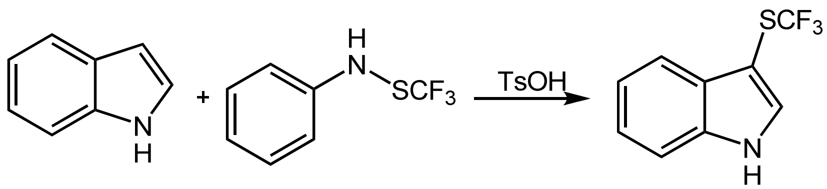


4. halogen–fluorine exchange reactions

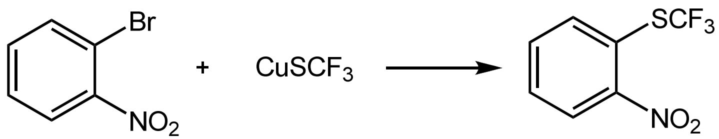


Direct trifluoromethanesulfanylation

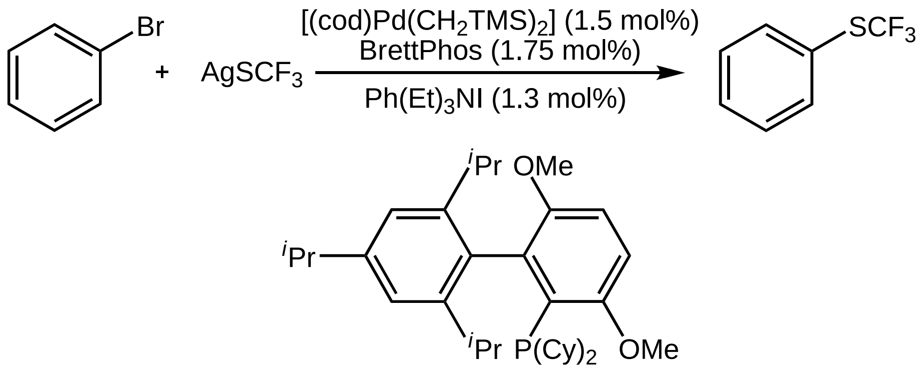
1. electrophilic substitution



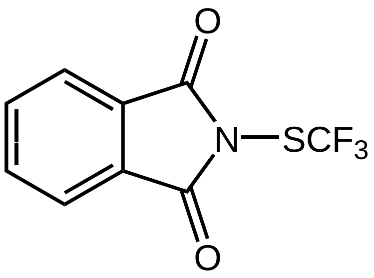
2. nucleophilic substitution



3. transition-metal catalyzed reaction

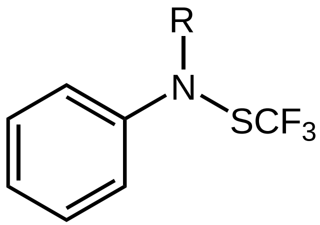


Three stable electrophilic SCF_3 sources



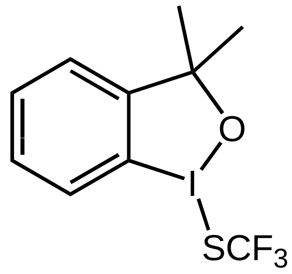
1

Munavalli, S.
2000



2

Billard, T.
2008



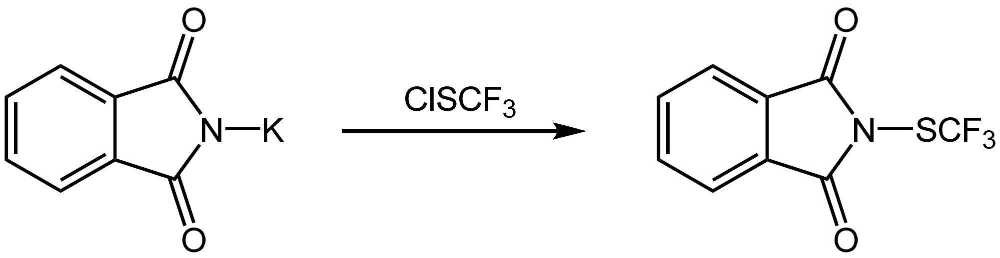
3

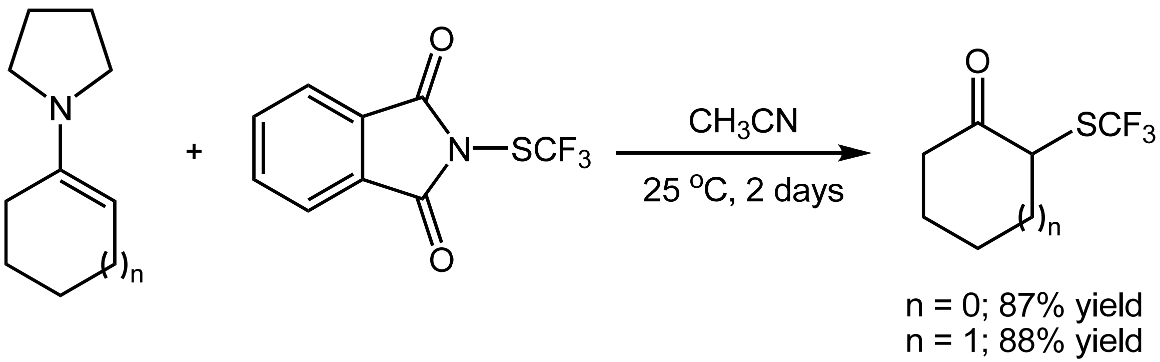
Shen, Q.
2013

Two gaseous and more toxic electrophilic SCF_3 sources

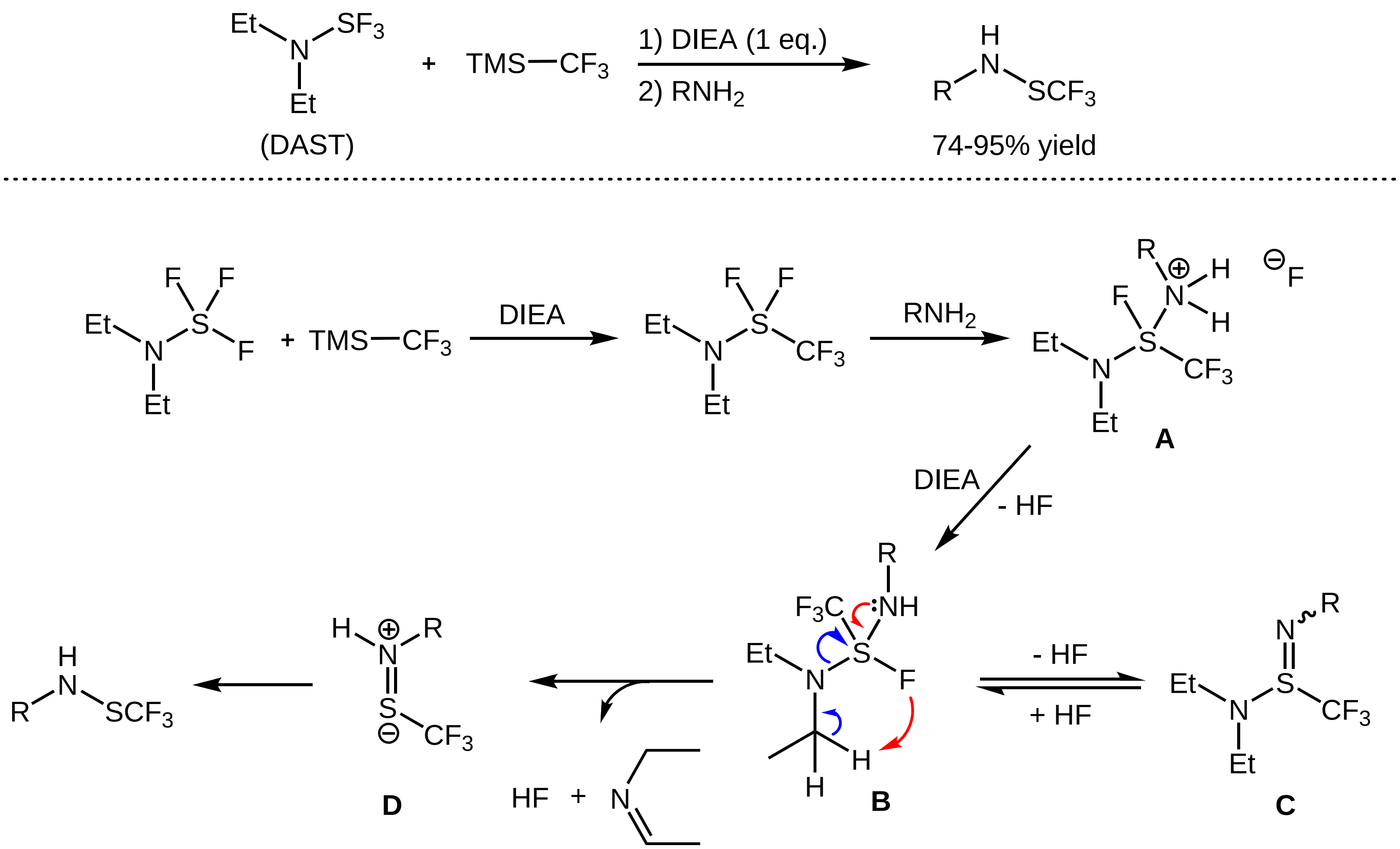
$ClSCF_3$ **$F_3CS\text{-}SCF_3$**

2. Trifluoromethylthiolation using stable electrophilic trifluoromethylthiolation reagents

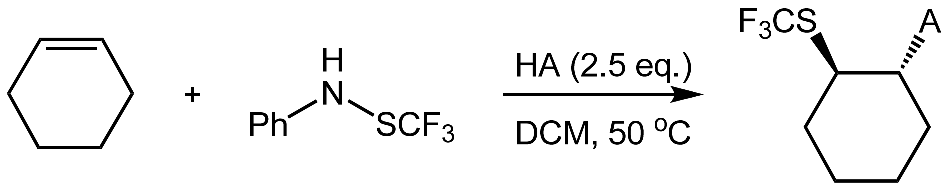


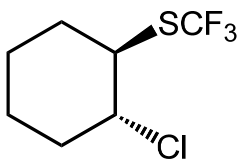


Munavalli, S. et al *Synth. Commun.* **2000**, *30,* 2847

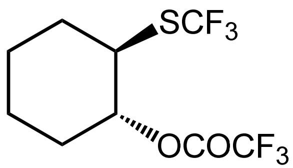


Billard, T. et al *J. Org. Chem.* **2008**, *73,* 9362

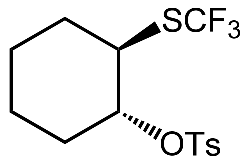




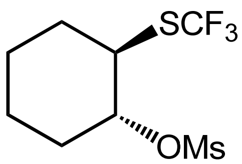
99% yield
(from HCl)



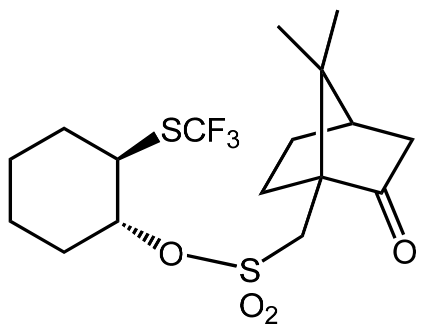
75% yield
(from CF_3CO_2H)



80% yield
(from TsOH)

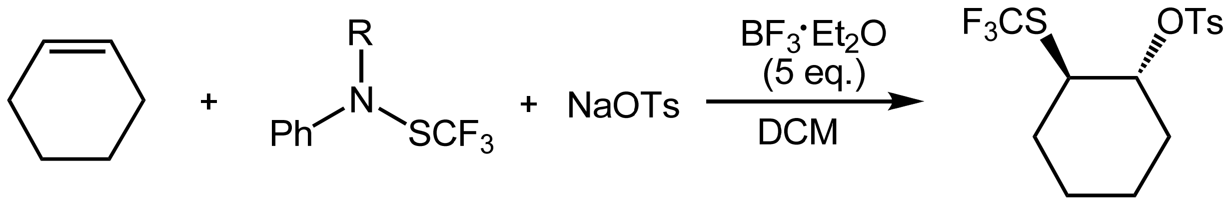


90% yield
(from CH_3SO_3H)

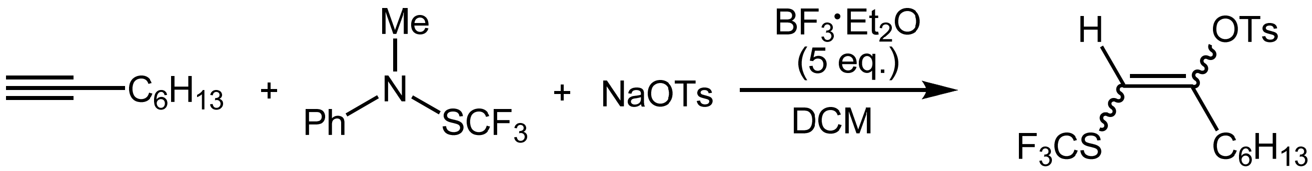


79% yield
(from *D*-CSA)

Billard, T. et al *Angew. Chem. Int. Ed.* **2009**, *48*, 8551

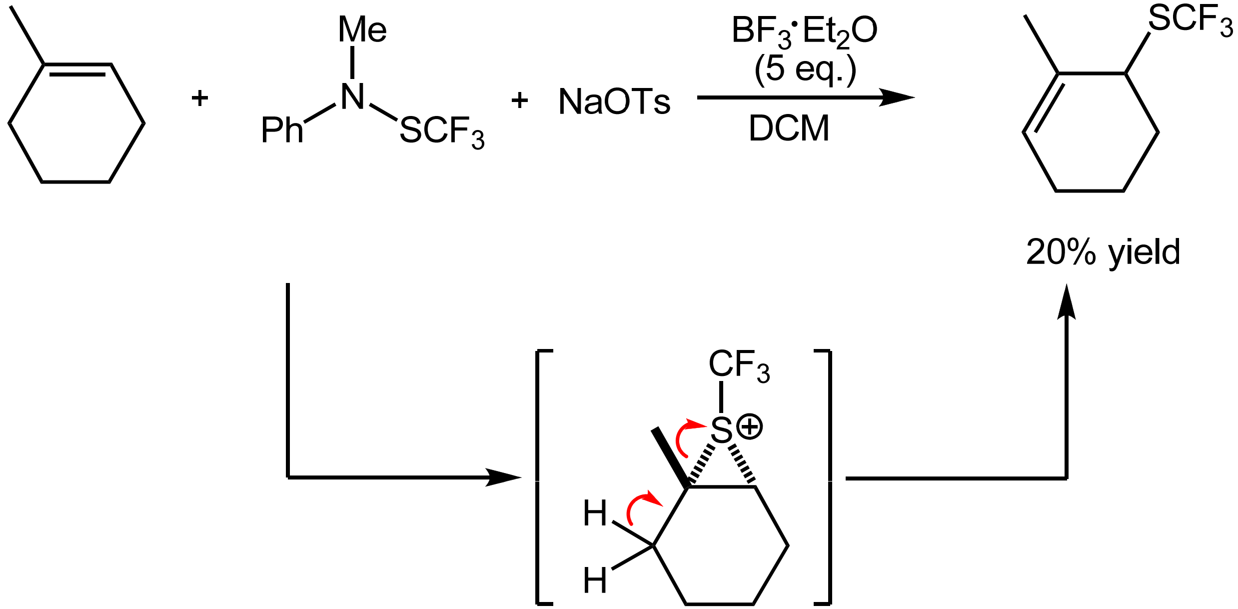


R = H: *t* = 18 h / crude yield 85%
R = Me: *t* = 4 h / crude yield 90%

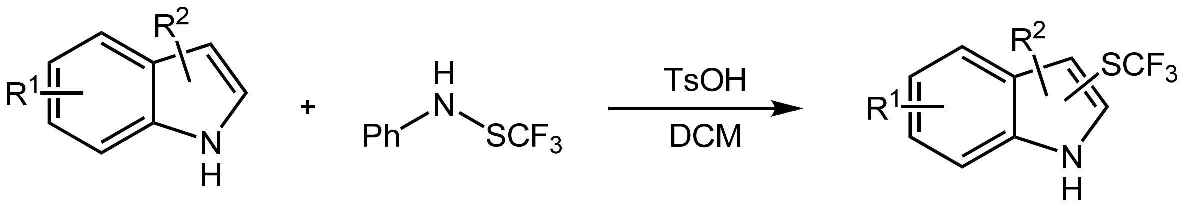


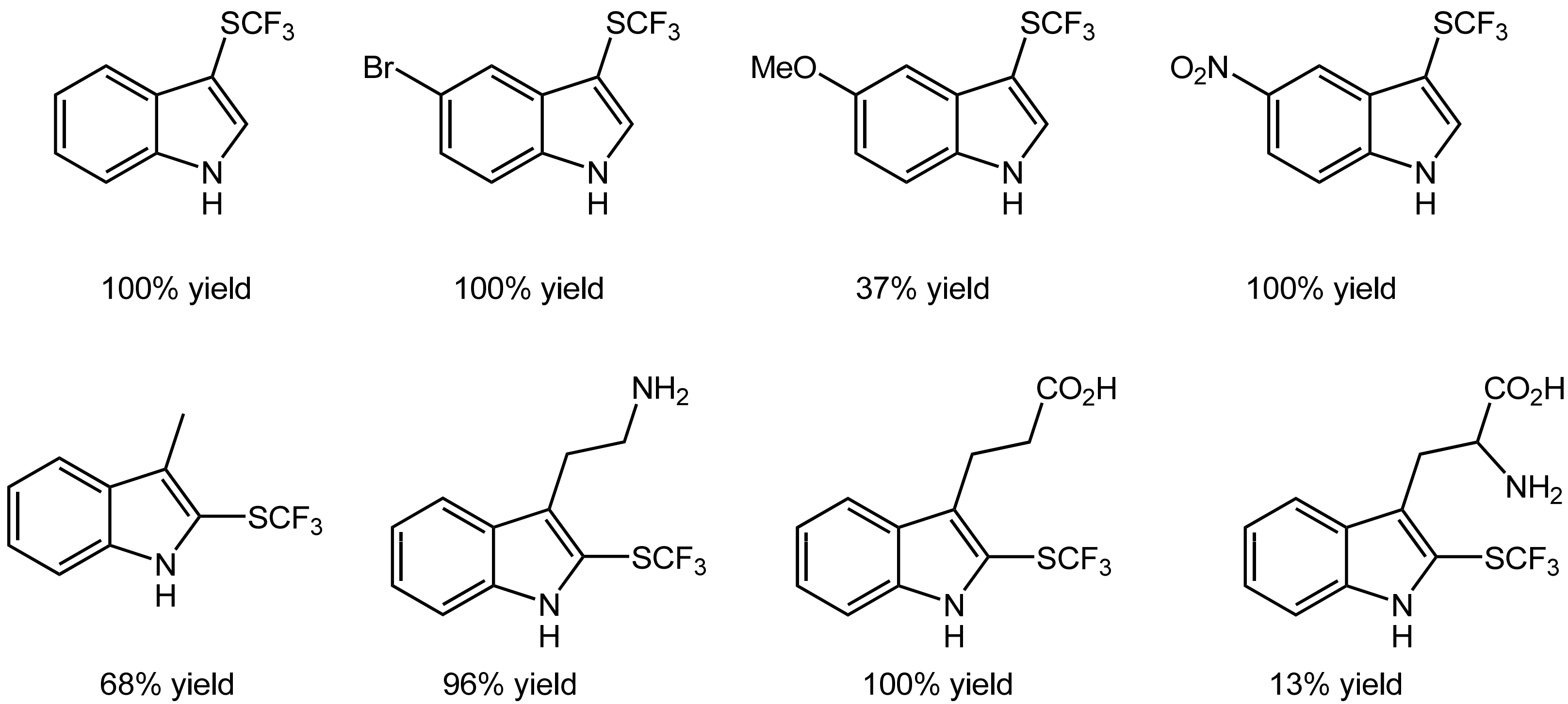
41% yield

Billard, T. et al *Angew. Chem. Int. Ed.* **2009**, *48*, 8551

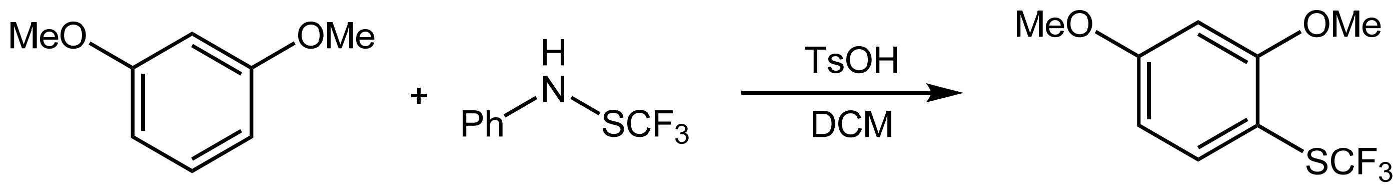


Billard, T. et al *Angew. Chem. Int. Ed.* **2009**, *48*, 8551



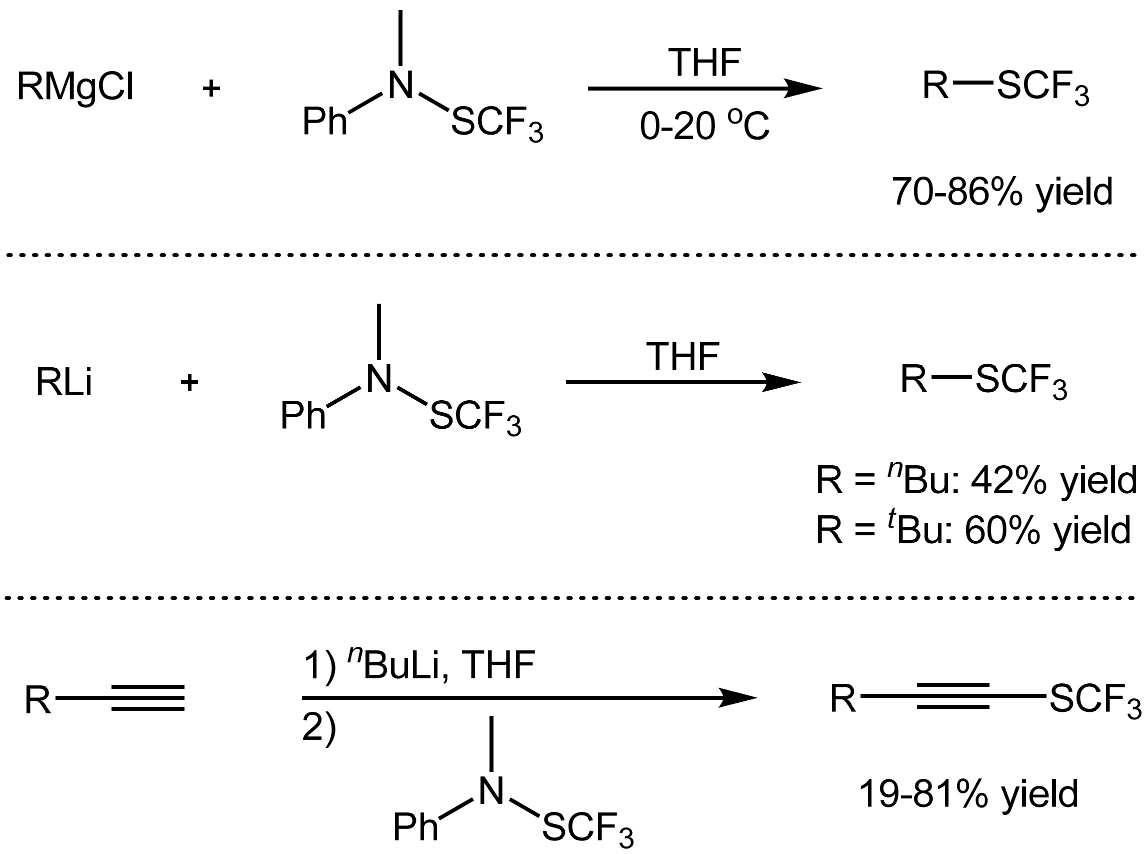


Billard, T. et al *J. Fluorine Chem.* **2012**, *134*, 160

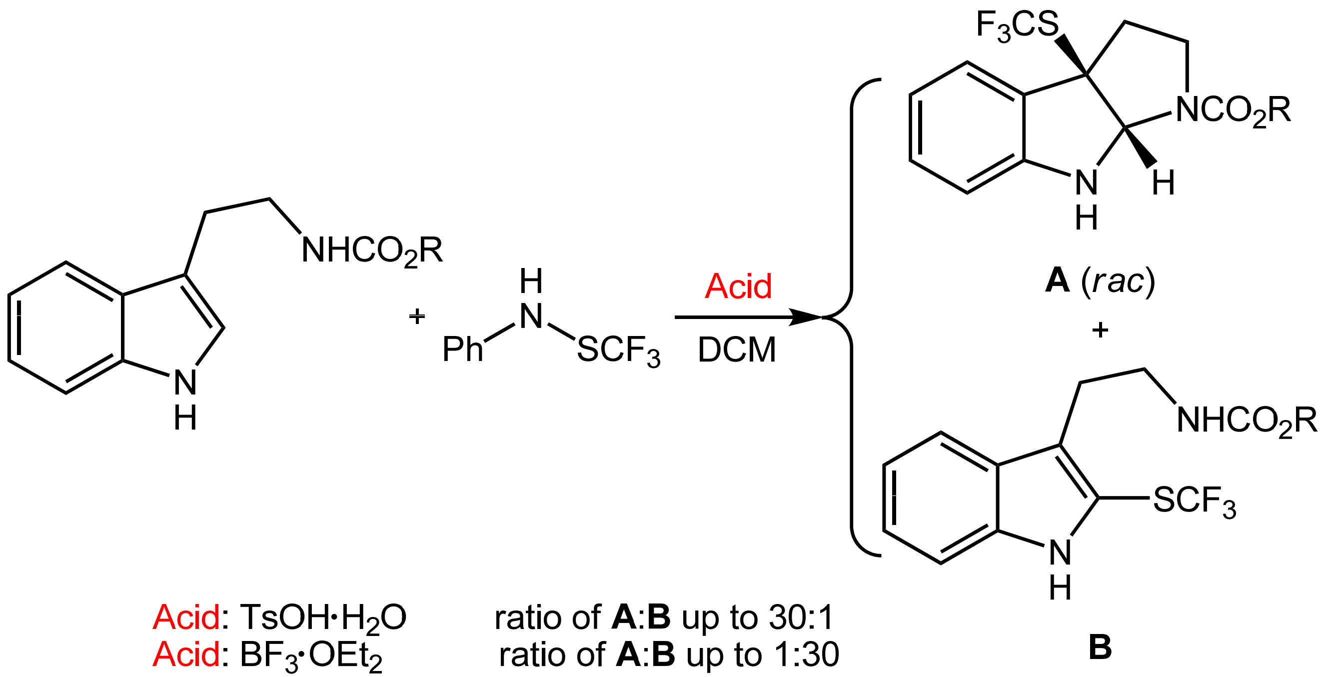


94% yield

Billard, T. et al *J. Fluorine Chem.* **2012**, *134*, 160

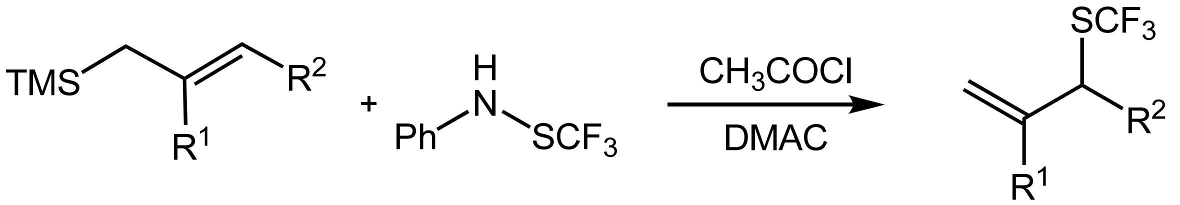


Billard, T. et al *Angew. Chem. Int. Ed.* **2012**, *51*, 10382



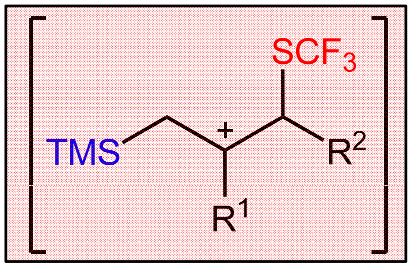
Acid: $TsOH \cdot H_2O$ ratio of **A**:**B** up to 30:1
Acid: $BF_3 \cdot OEt_2$ ratio of **A**:**B** up to 1:30

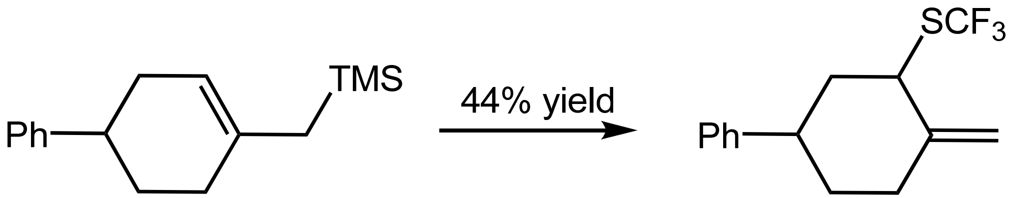
Qing, F.-L. et al *J. Org. Chem.* **2012**, *77*, 7538



R^1 = aryl. alkynyl, alkyl
R^2 = H, alkyl

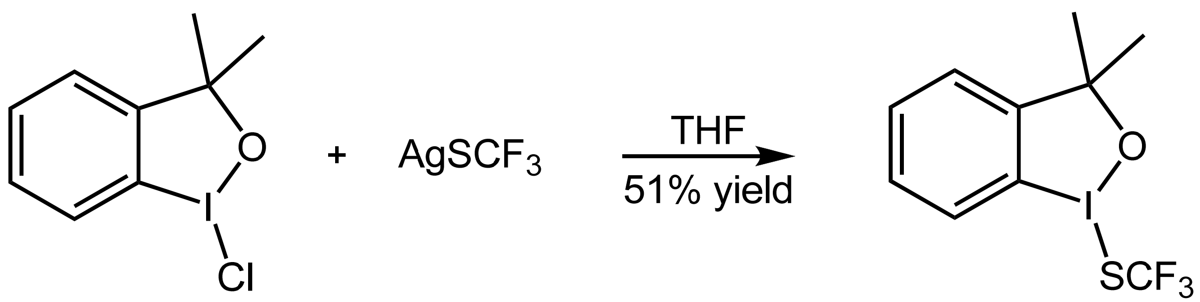
17 examples
40-89% yields





Qing, F.-L. et al *Org. Lett.* **2013**, *15*, 894

$$AgF + CS_2 \xrightarrow[\text{85\% yield}]{CH_3CN,\ 80\ ^{o}C} AgSCF_3$$



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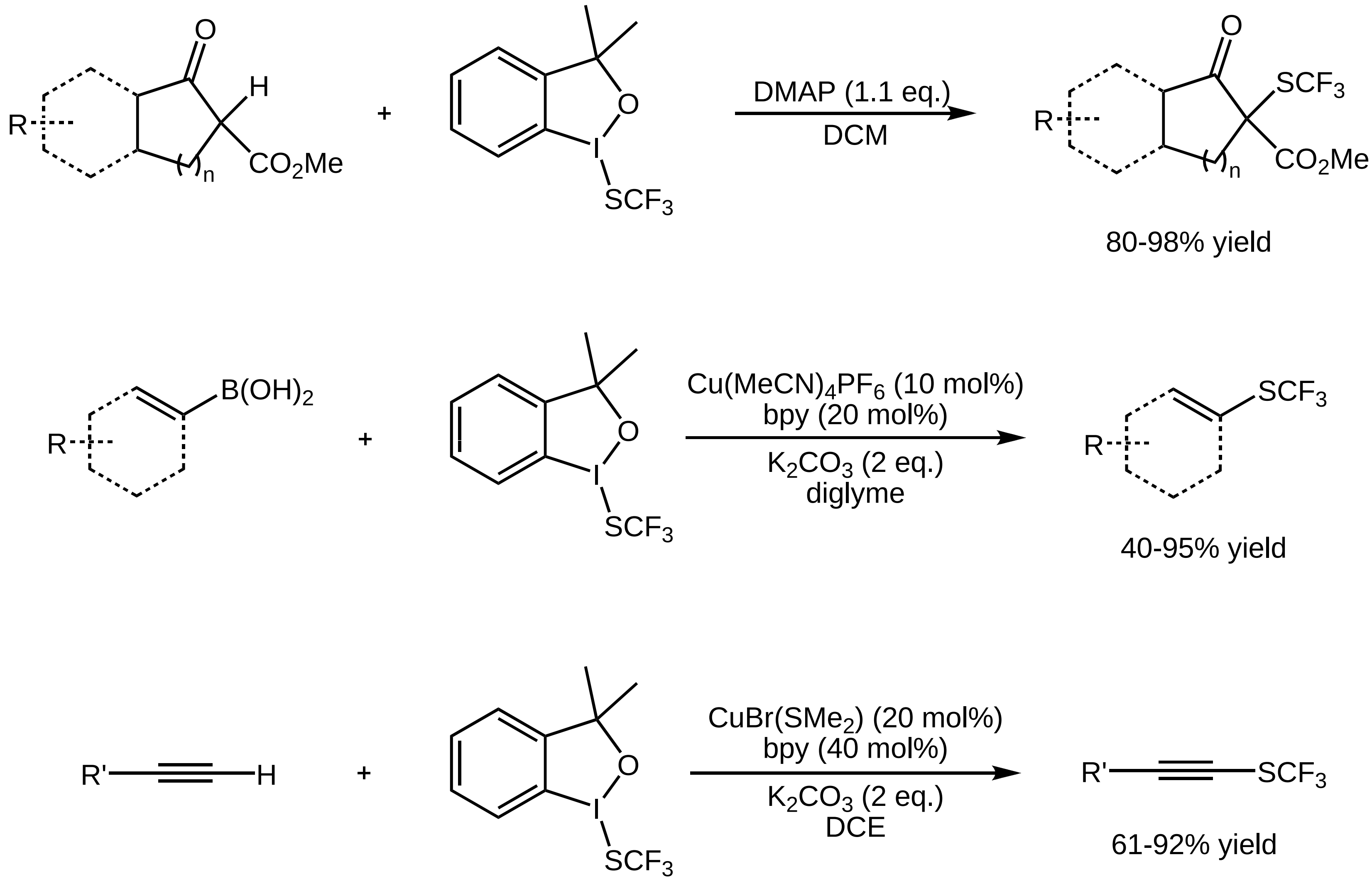
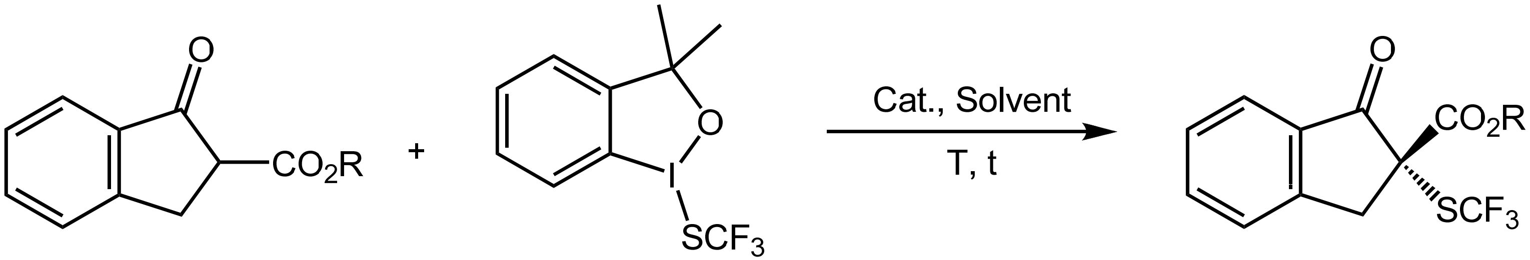
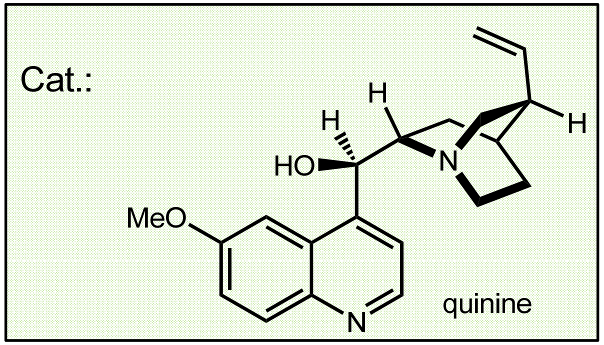


Shen, Q. et al *Angew. Chem. Int. Ed.* **2013**, *52*, 3457

3. Asymmetric trifluoromethylthiolation





Entry	R	Solvent	T [°C]	t [h]	Yield [%]	Ee [%]
1	Me	THF	RT	12	90	42
2	Et	THF	RT	12	57	49
3	Ad	THF	RT	24	44	90
4	Ad	PhMe	RT	24	66	92
5	Ad	PhMe	40	36	91	92

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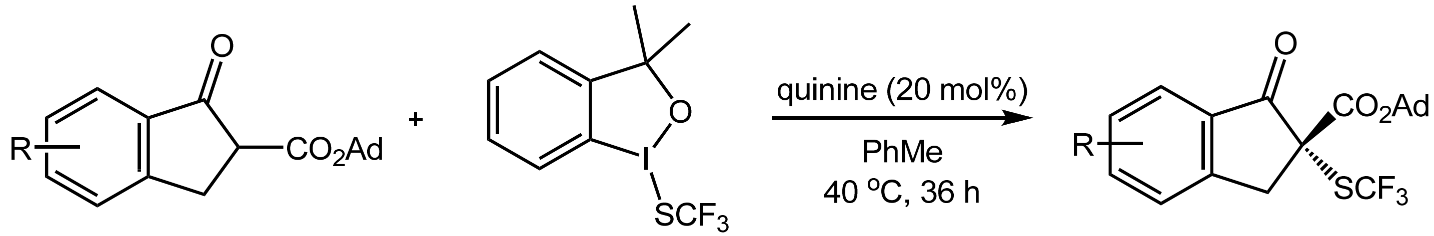
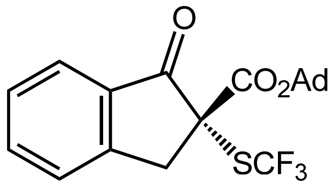
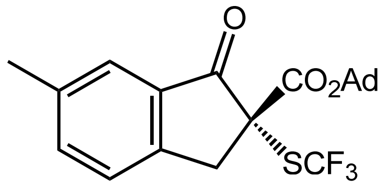
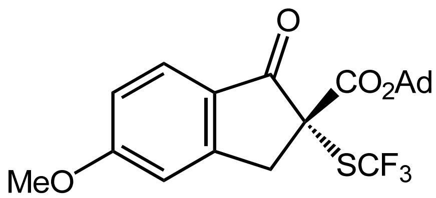




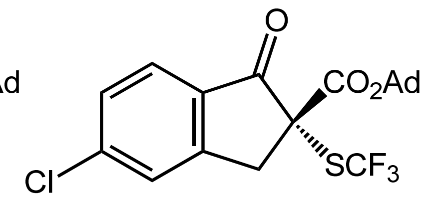
90% yield, 92% ee



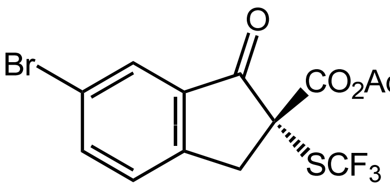
97% yield, 86% ee



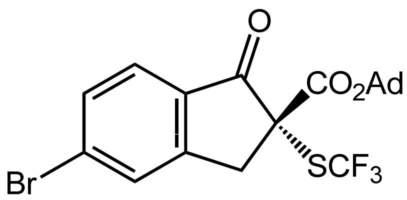
95% yield, 94% ee



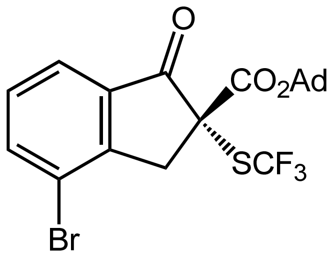
87% yield, 92% ee



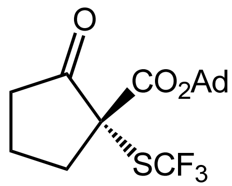
83% yield, 93% ee



81% yield, 92% ee



82% yield, 89% ee



95% yield, 94% ee

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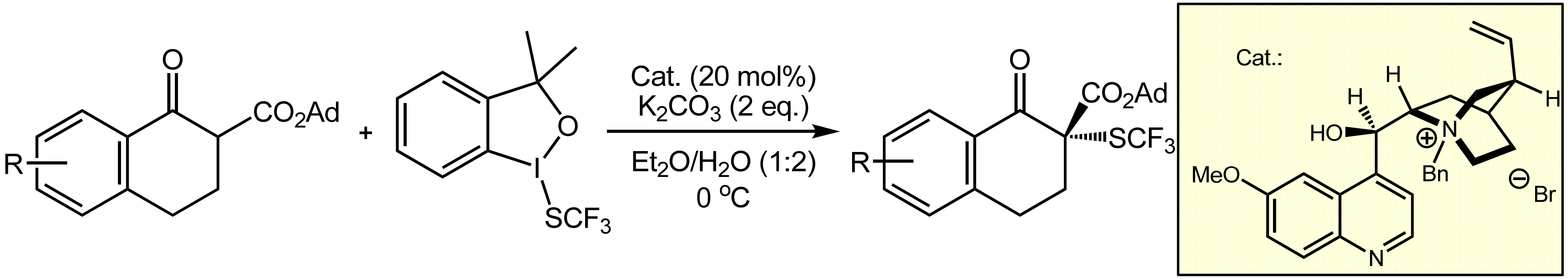
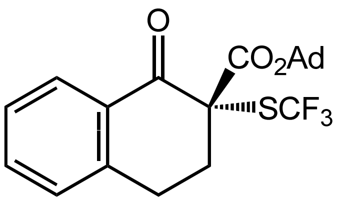
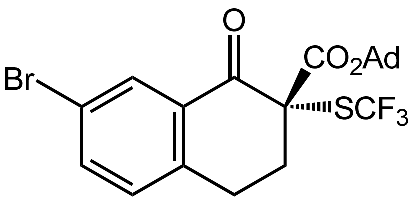
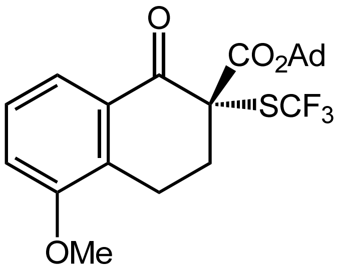




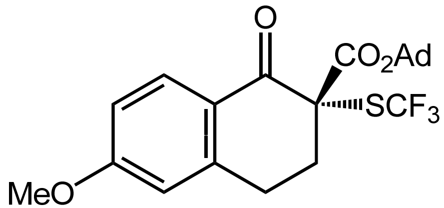
93% yield, 80% ee



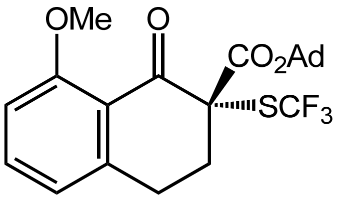
84% yield, 70% ee



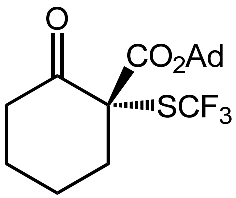
90% yield, 77% ee



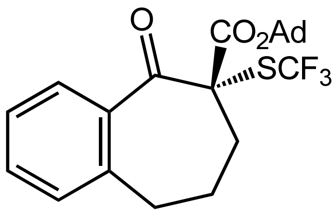
91% yield, 66% ee



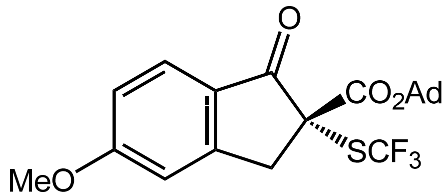
91% yield, 73% ee



49% yield, 64% ee



88% yield, 96% ee



87% yield, 20% ee

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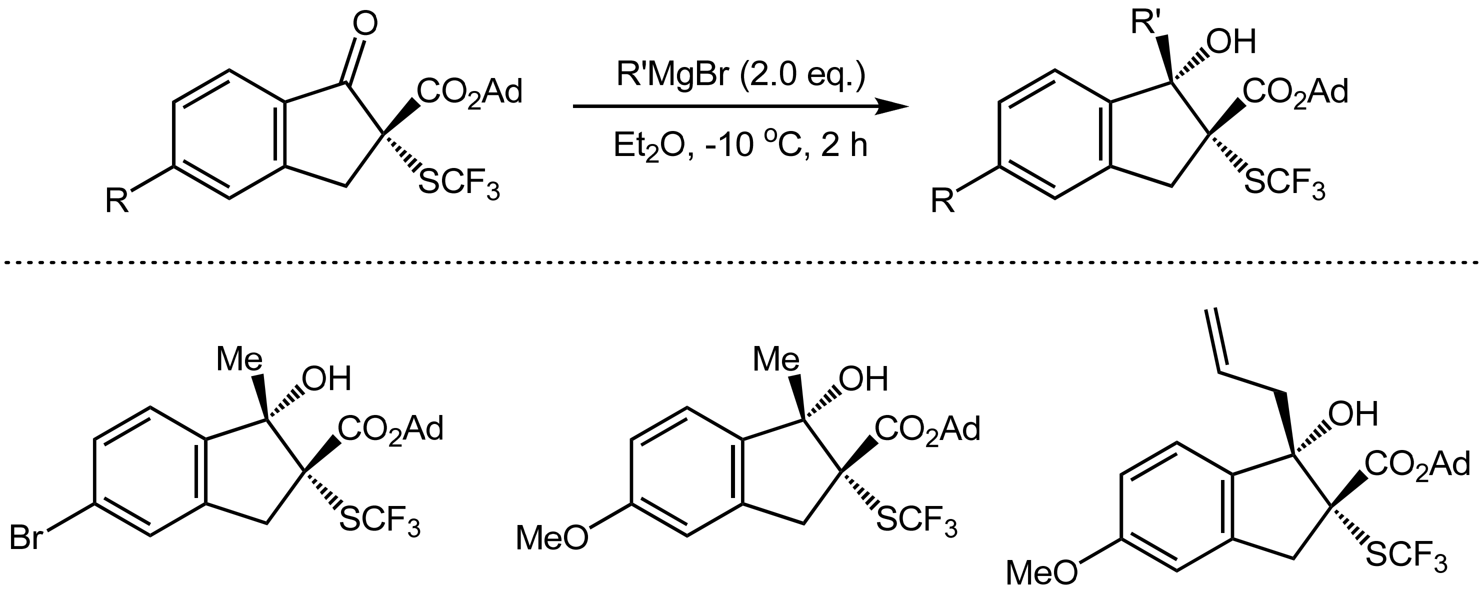

80% yield, 93% ee
>20:1 dr

74% yield, 92% ee
>15:1 dr

89% yield, 92% ee
1.83:1 dr

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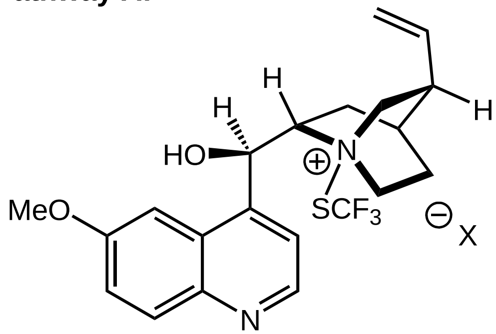
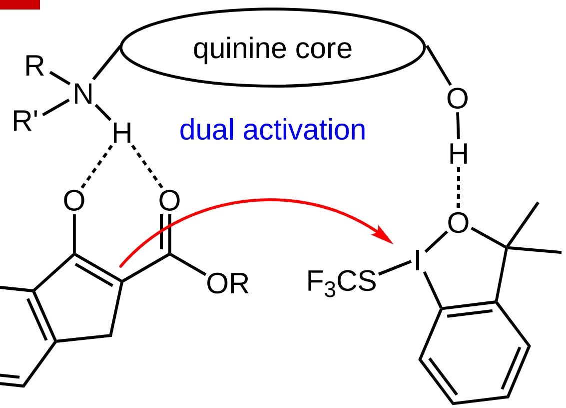
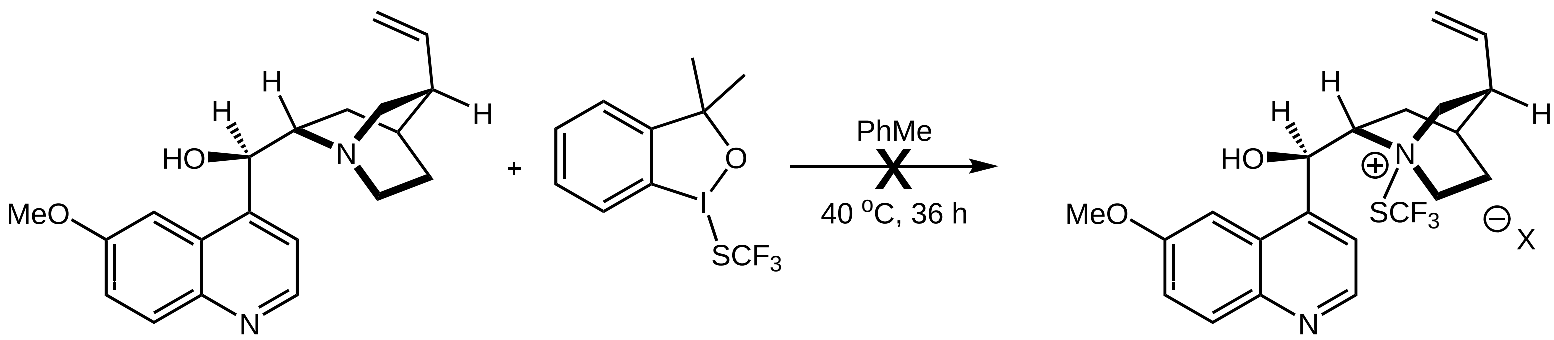
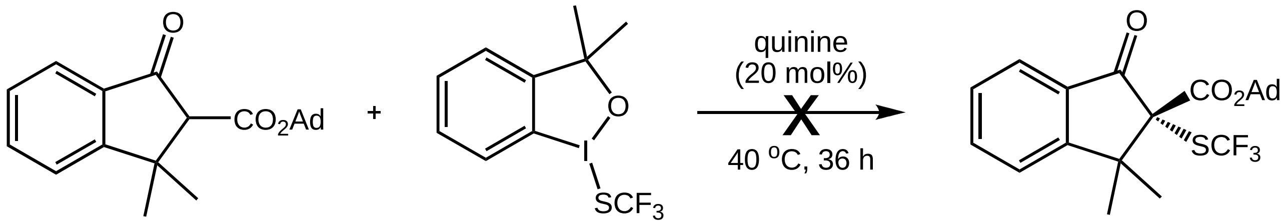
Pathway A:



Pathway B:







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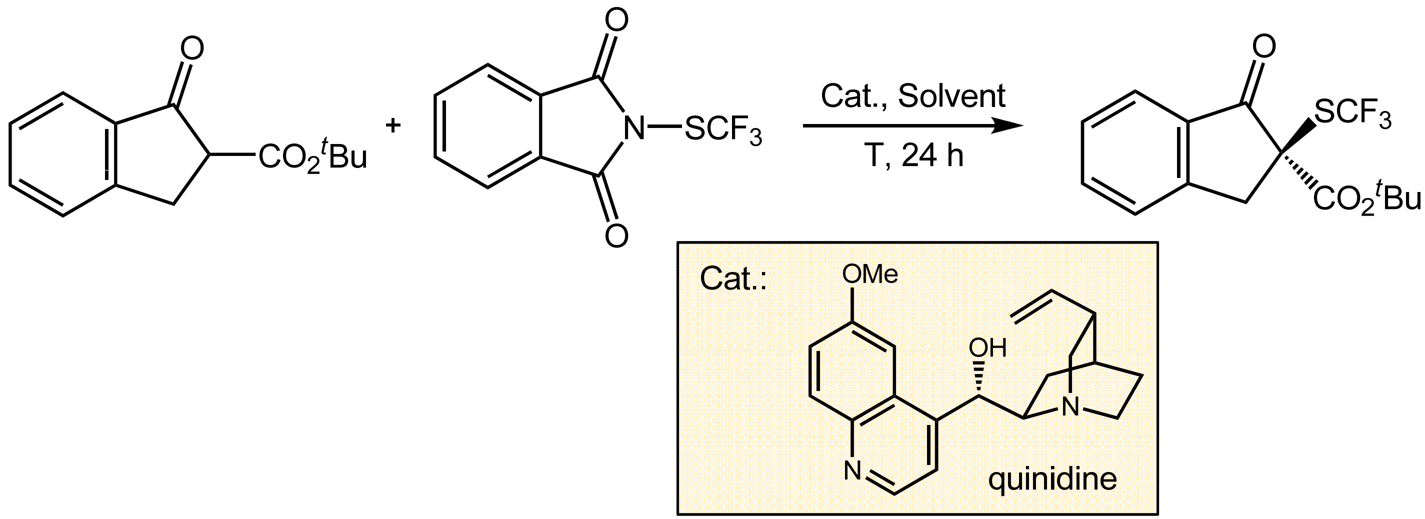

Entry	Solvent	T [ºC]	Yield [%]	Ee [%]
1	PhMe	0	95	85
2	DCM	0	98	95
3	CH_3Cl	0	94	94
4	DCE	0	98	94
5	THF	0	94	20
6	DCM	-75	93	98

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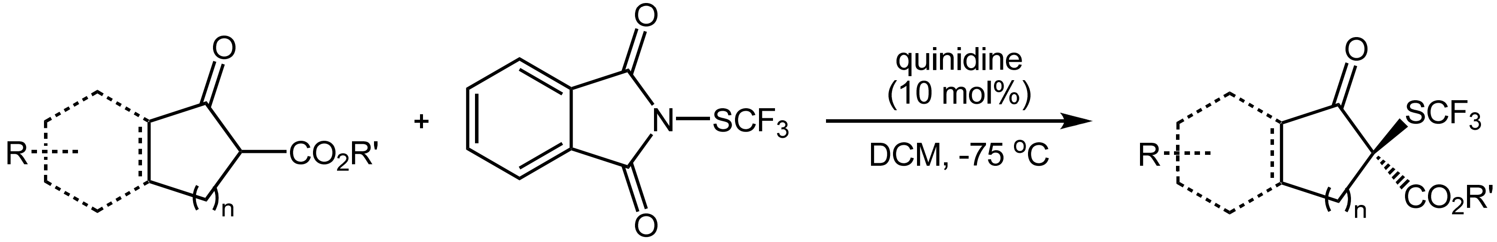
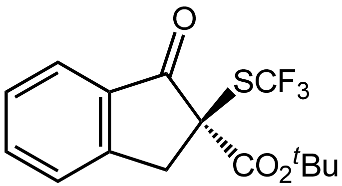
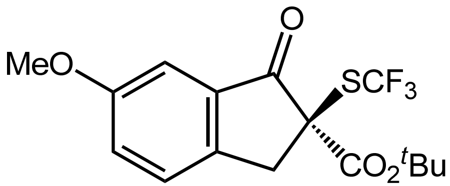
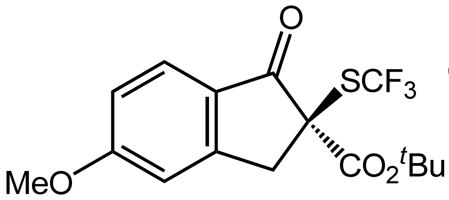




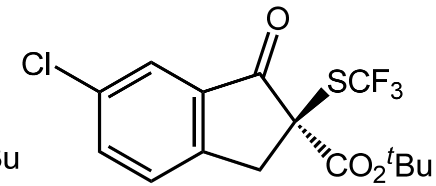
95% yield, 98% ee



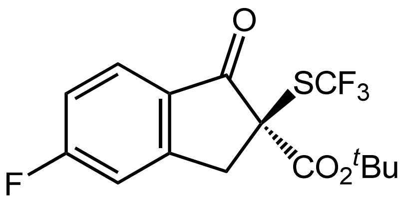
87% yield, 98% ee



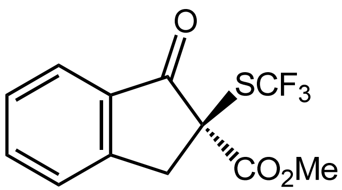
98% yield, 98% ee



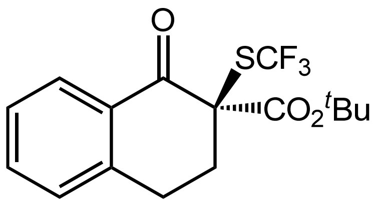
96% yield, 98% ee



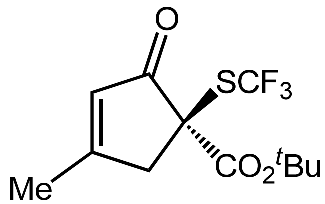
94% yield, 99% ee



87% yield, 94% ee



46% yield, 95% ee
(0 °C, 7 days)



69% yield, 94% ee

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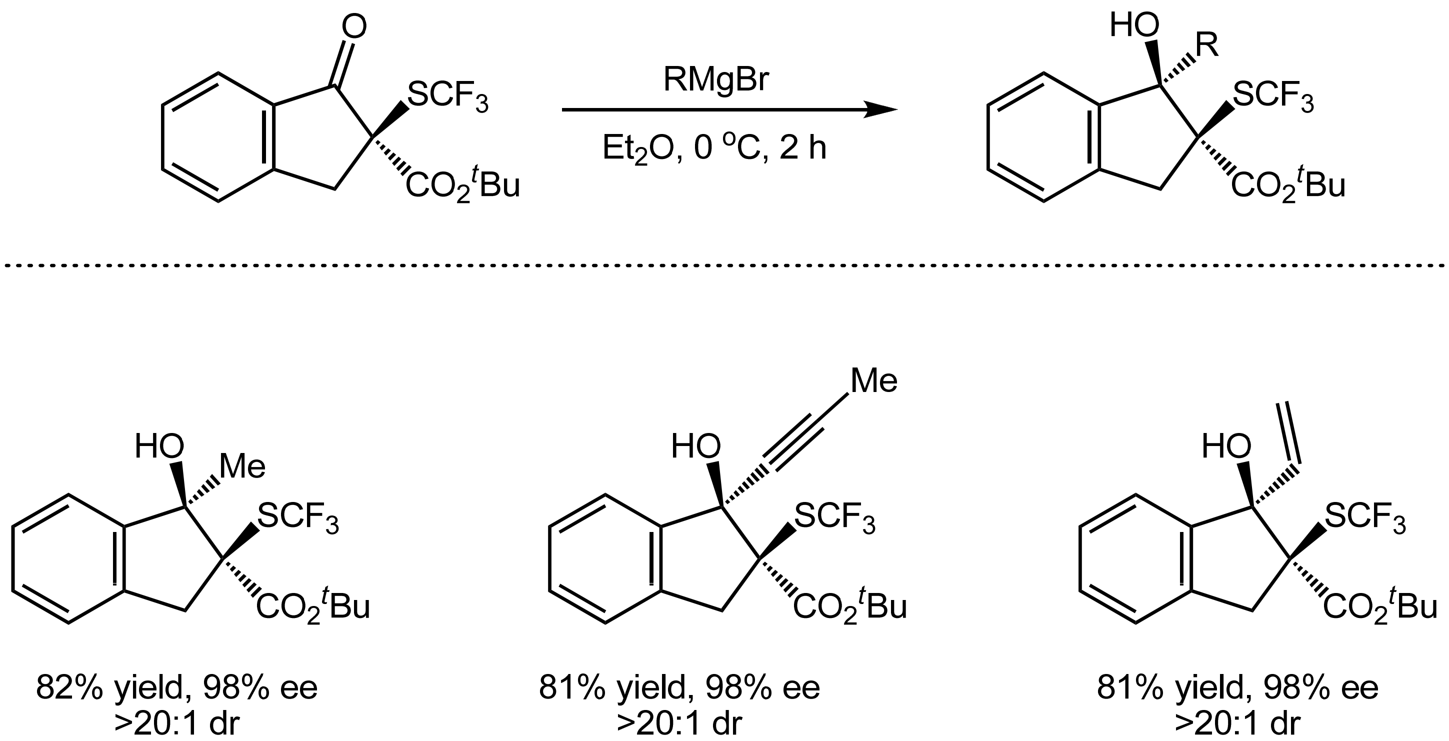

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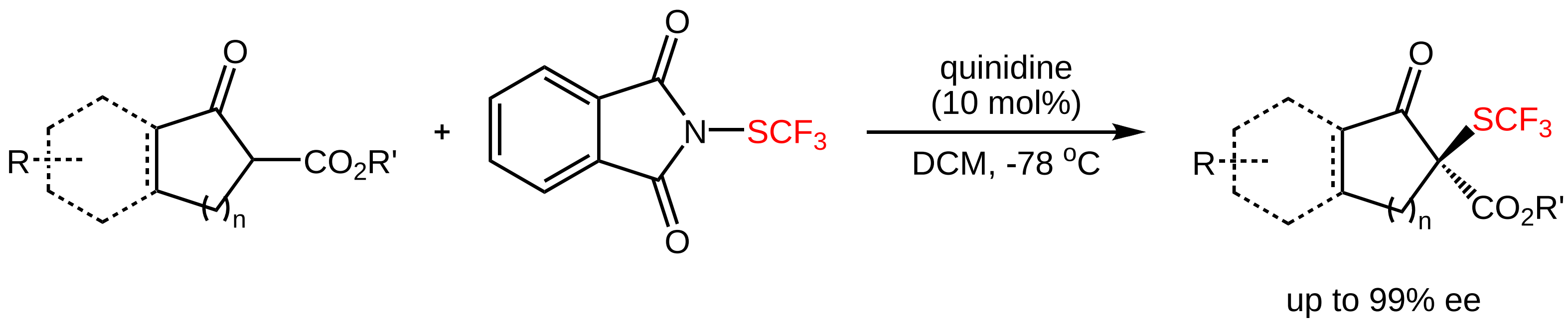
5. Summary



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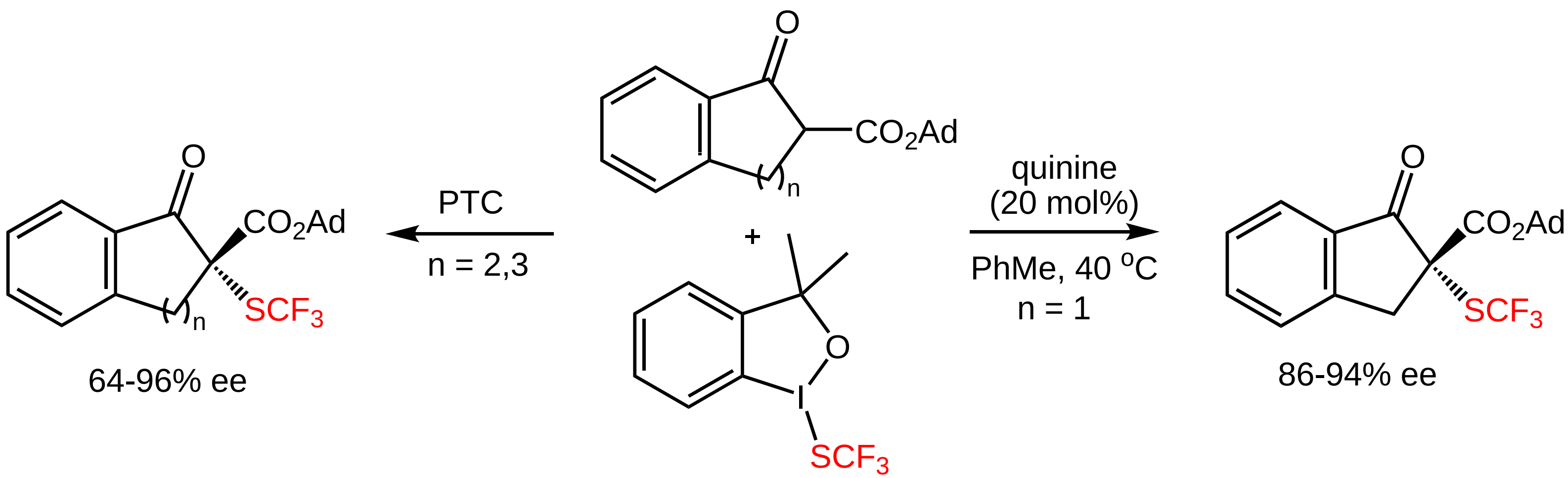

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The incorporation of an SCF_3 group into small molecules is of great interest to the pharmaceutical and agrochemical industries, because the high lipophilicity and high electron-withdrawing character of the SCF_3 group may have beneficial effects on the pharmacokinetics of drug molecules. Thus, the development of efficient methods for the introduction of a SCF_3 group into organic compounds has recently become a subject of intense study and tremendous progress has been achieved in the transition-metal-catalyzed trifluoromethylthiolation of aryl, alkenyl, or alkynyl substrates under mild conditions. In particular, there has been a growing interest in the stereoselective introduction of SCF_3 groups to generate chiral centers. While there is a growing number of methods for the catalytic enantioselective trifluoromethylation, to the best of our knowledge, the analogous catalytic asymmetric direct trifluoromethylthiolation has never been reported.

In summary, we have developed the highly enantioselective trifluoromethylthiolation of β-ketoesters catalyzed by a chiral Lewis base or a phase-transfer catalyst. The reaction employs commercially available and fully recyclable catalysts and involves a simple experimental procedure. In addition, the reaction constitutes a practical and broadly applicable approach toward chiral building blocks with quaternary stereocenters that bear an SCF_3 group, and might lead to some drug candidates with high bioactivity. Further development of relevant catalytic systems and the elucidation of the mechanism of this reaction are in progress in our laboratory and will be reported in due course